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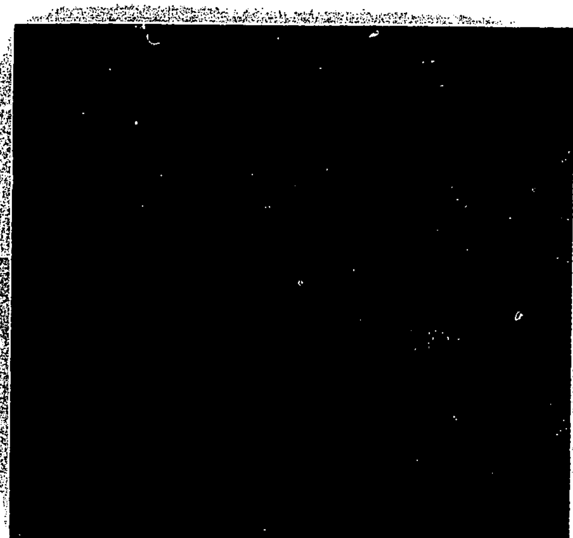
Sunlight and Skin Cancer

Although most skin cancers appear in older people, the damage often begins decades earlier, when the sun's rays mutate a key gene in a single cell

by David J. Leffell and Douglas E. Brash



ANTI-CANCER COUNCIL OF VICTORIA

YOUNG BATHERS, such as these Australian children, may predispose themselves to skin cancer as they play. Yet only one youngster here is taking precautions.

In 1775 the British physician Percivall Pott reported a curious prevalence of ragged sores on the scrotums of many chimney sweeps in London. Other doctors might have concluded that the men were afflicted with a venereal disease that was then rampant throughout the city. But Pott was more astute. He realized they were in fact suffering from a type of skin cancer. Pott's discovery was a medical milestone. By observing that men continually exposed to coal tar were "peculiarly liable" to this form of cancer, he documented for the first time that cancer could be caused by an external agent rather than by internal factors.

More recently, investigators have identified another link between the environment and skin cancer, but this time the agent is much more ubiquitous. It is nothing less than light from the sun. The painstaking efforts of dozens of researchers have revealed a great deal about how solar rays contribute to the development of an astonishingly high number of skin cancers every year.

In the U.S. alone, about a million new cases occur annually, rivaling the incidence of all other types of cancer combined. Skin cancer typically takes one of three forms corresponding to the three major types of skin cells: basal cells, squamous cells and melanocytes. Cancer of melanocytes, called malignant melanoma, is the most lethal variety—and perhaps the most mysterious to researchers attempting to understand how these tumors are triggered. Fortunately, it is also the least common. In the U.S. there will be about 38,000 new cases of melanoma this year and approximately 7,000 deaths from the disease. The two other forms, together called nonmelanoma skin cancer, account for the balance of the cases but kill a much smaller percentage of the affected population. A few thousand people are expected to die in the U.S. during 1996 from nonmelanoma (almost exclusively squamous cell) skin cancer.

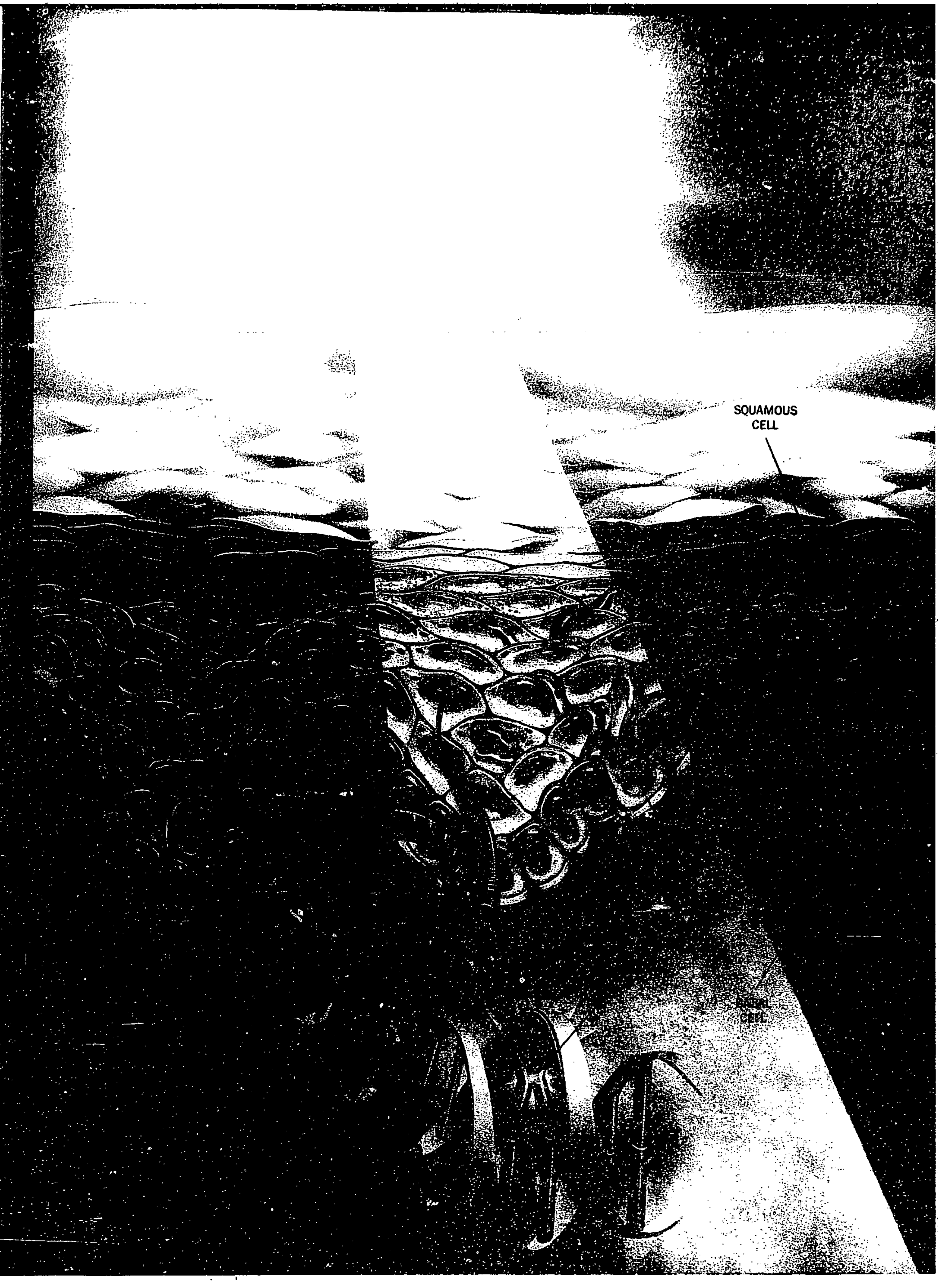
If caught early, most cases of nonmelanoma skin cancer are easily treated in a doctor's office under local anesthesia. Such cancers can be cured by a variety of simple techniques, including scraping, burning, freezing or surgically excising the malignant tissue. Even melanoma, if diagnosed when the tumor is still less than one millimeter thick, can usually be cured by simple excision. But because skin cancer plagues members of all age groups, and because it can become disfiguring and deadly if left untreated, medical researchers have mounted an immense scientific effort over the years to unravel the mechanisms that cause this disease. Curiously, an accident of history contributed much to that quest.

An Accidental Experiment

At the time Pott was studying scrotal cancer, Georgian England had a legal system that inflicted severe punishments for petty crimes: forgery or thievery often resulted in a death sentence. But a backlash against the harshness of execution for such misdemeanors soon led to milder sentences—and thus to the overcrowding of jails. To unburden the country's prisons, the House of Commons voted to banish criminals to remote locales beginning in the 1780s. The destination of choice was a little known shore bordering the South Pacific Ocean. Within a few decades, the east coast of Australia was populated with British and Irish men and women. Those early colonists often shared the Celtic features of fair skin and light hair, and today their descendants predominate on that southern continent.

HUMAN SKIN includes three major cell types, all of which are susceptible to sunlight-induced cancer. Near the base of the epidermis lie round, basal cells. Closer to the surface are flattened, squamous cells. Melanocytes (cells that produce the protective pigment melanin) are interspersed in the basal layer and have numerous extensions that reach outward. Solar rays, which can penetrate well below the surface of the skin, damage segments f a cell's DNA that are particularly vulnerable to ultraviolet light. Damage t a gene called *p53* appears crucial to basal cell and squam us cell skin cancers.

AUDRA GERAS



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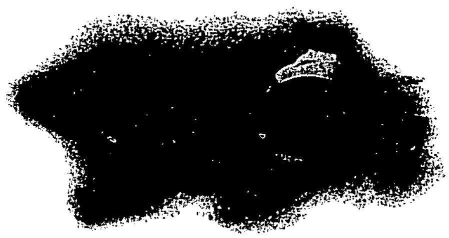

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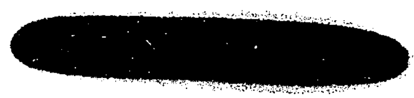

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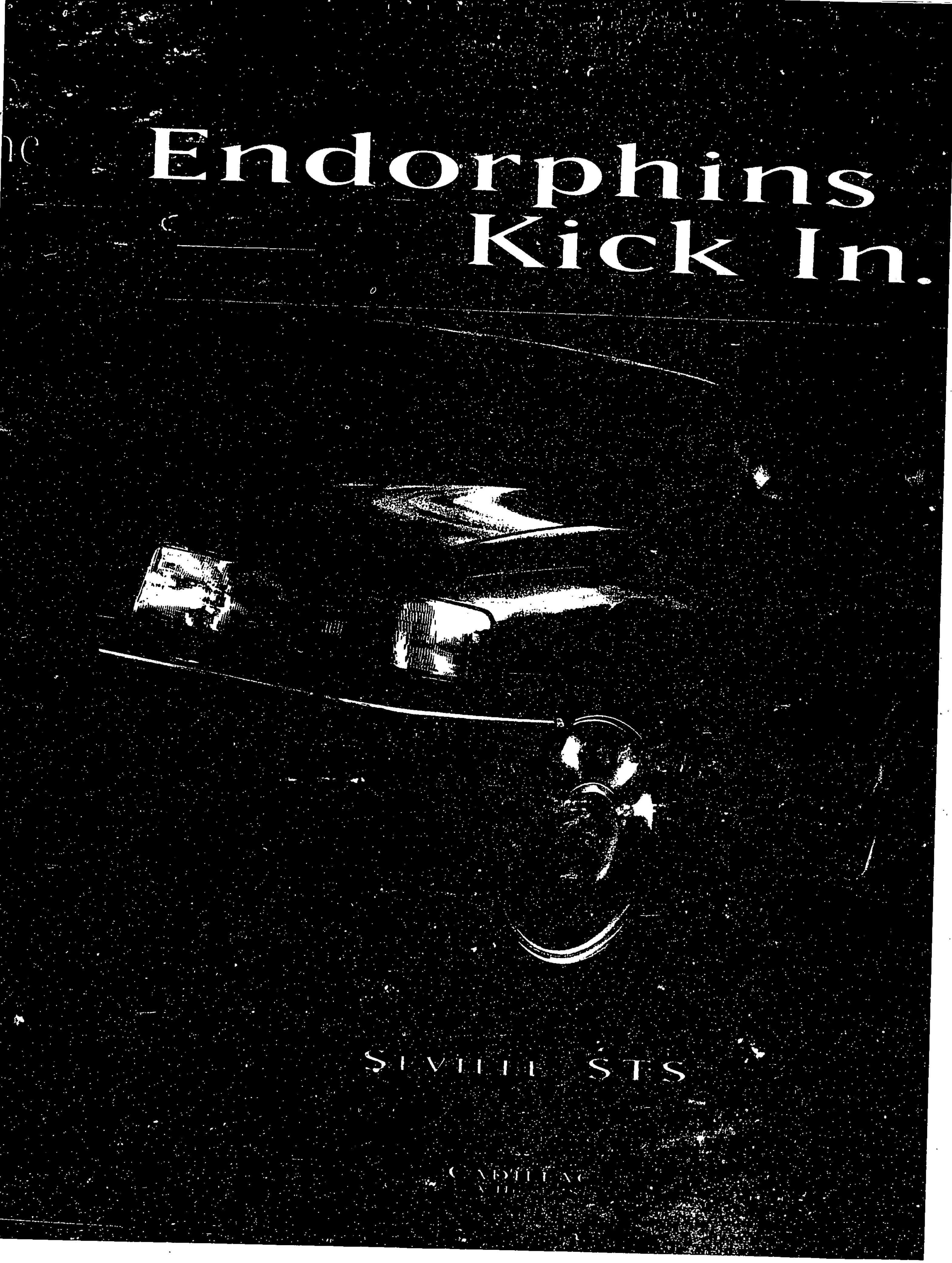
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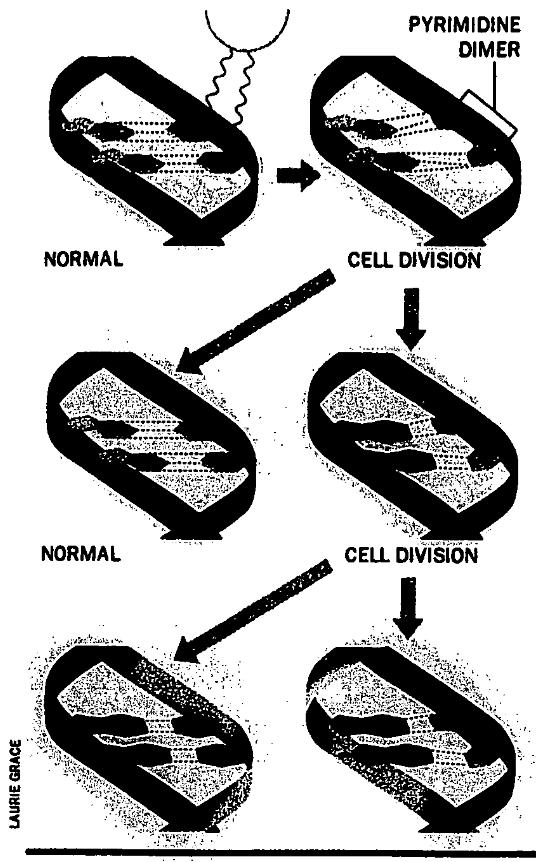
How Sunlight Can Cause a Permanent Mutation



ULTRAVIOLET LIGHT can break chemical bonds in adjacent pyrimidine bases, often at a point on the DNA strand where two cytosines (*C*) occur. New bonds then form (*red*), linking the disrupted bases together in a so-called pyrimidine dimer.

REPLICATION requires that a cell separate the paired DNA strands (*green* and *blue*), each of which is used as a template to construct a new strand (*purple*)—by mating guanine (*G*) with cytosine and adenine (*A*) with thymine (*T*). The strand unaffected by sunlight produces normal DNA (*left*), but the strand containing the pyrimidine dimer pairs disturbed *C*s with *A*s instead of matching them properly with *G*s.

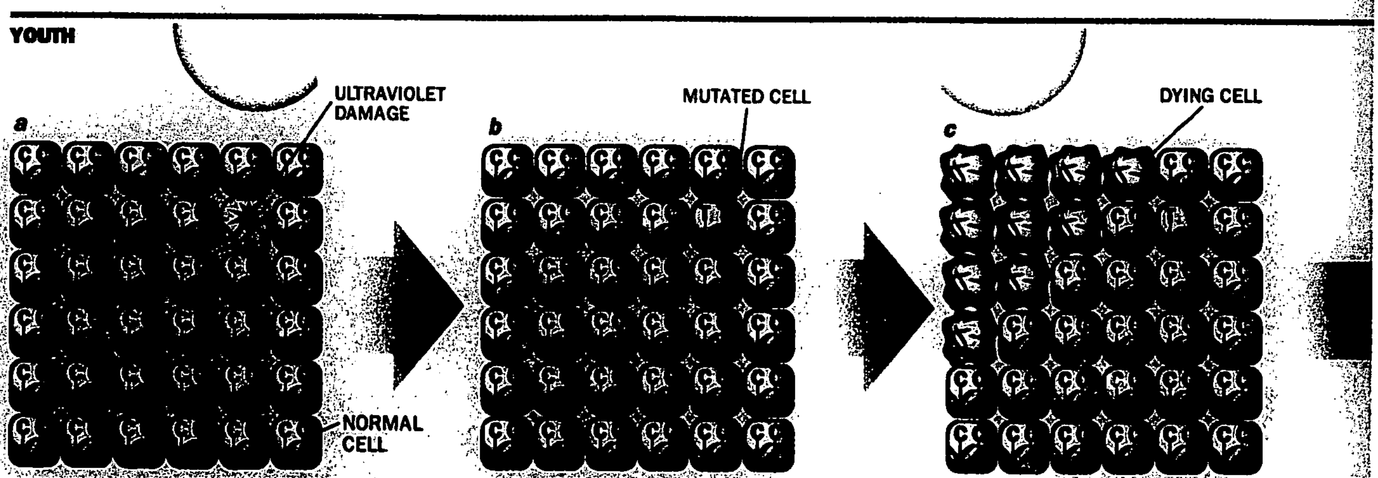
CONTINUED REPLICATION repeats the error, mating the dimer once more with a pair of *A*s (*right*). On the opposite strand (*left*), these *A*s are matched with *T*s, creating a genetic mutation. The dimer may eventually be eliminated by "excision repair," but the *C*-to-*T* mutation is permanent. When such a mutation falls within a cancer-related gene, the cell becomes prone to malignancy.

What began as an 18th-century attempt at penal reform ultimately culminated in a de facto large-scale experiment on the links between complexion, solar radiation and skin cancer. With their fair skin continually exposed to intense sun, whites in Australia now have the highest rate of all kinds of skin cancer of any people in the world. Their British relatives, who live under cloudy northern skies, are more fortunate. They have a relatively low risk of acquiring these malignancies—as do Australian Aborigines, who with much darker skin are rarely affected by sun-induced cancers of the skin.

Investigators recognized as early as 50 years ago that the Australian experience implicated strong sun and fair skin as important risk factors for skin cancer. But for decades scientists were unable to explain what the sun was actually doing to skin cells to make them become cancerous. Clarifying that mystery required more than an accidental experiment on a sun-drenched continent. It took years of study in research laboratories of molecular biologists around the world before the details of that process began to be uncovered.

When the two of us started to attack this problem in the late 1980s, two types of insults from the sun seemed equally suspect. In one category were mutations of specific genes within skin cells. A cell may reproduce excessively if a mutation either turns a normal gene into an overzealous growth promoter (an oncogene) or inactivates a gene that normally limits cell growth (a tumor suppressor gene). The other class of causes we considered at the outset included more widespread events—ones that would affect every sun-exposed cell. For example, the sun's radiation might suppress the skin's immune response (reducing its natural ability to eliminate tumor cells) or directly stimulate cell division. With such diverse explanations possible, we knew that isolating the causes of skin cancer would not be easy.

But we were guided by the knowledge that the damaging effects of sunlight can occur many years before tumors appear. Such delayed effects were most clearly demonstrated in studies undertaken by Anne Kricker, then at the University of Western Australia, Robin Marks of the



GROWTH OF A NONMELANOMA SKIN TUMOR is thought to involve sunlight altering the *p53* gene in a squamous or basal cell of the skin (*a*). The mutation that results (*b*) destroys the ability of genetically injured cells to delay replication until they have repaired their DNA. The *p53* mutation also prevents such cells from killing themselves when damaged beyond

Anti-Cancer Council of Victoria and their colleagues. They noted that people who had emigrated from cloudy England to sunny Australia before the age of 18 acquired the higher Australian incidence of skin cancers, but if they moved when they were older, they retained the native risk.

These findings indicated that Australian skin cancer patients must have received a critically high dose of sunlight years before the appearance of tumors (which rarely occurred before middle age). Widespread events, such as immunosuppression, last for only a few days after the injurious radiation ceases. But genetic changes persist (being passed from one generation of cells to another). Looking for genetic changes therefore seemed a more promising avenue for our research. So we began a hunt for sunlight-induced mutations that could occur early in life and set the stage for the development of skin cancer much later on.

A Signature Mutation

That search was daunting. The DNA in a human cell contains as many as 100,000 genes, and each gene typically includes thousands of nucleotides (the building blocks of DNA)—only some of which would be likely to bear traces of sun-induced damage. And even if we managed to identify mutations in skin cancer samples, how could we be sure that sunlight had caused them? Fortunately, other investigators had given us a useful clue by finding that ultravi let B radiation—long suspected to be the carcinogenic factor in sunlight—had a characteristic signature.

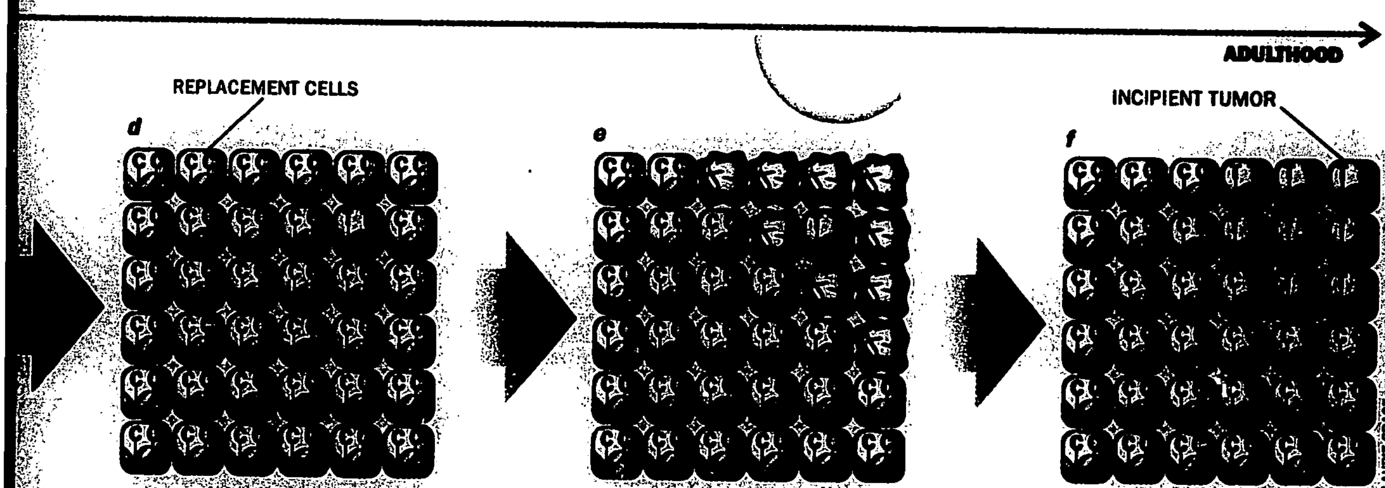
After studying everything from viruses to human cells, groups of researchers from Switzerland, France, Canada and the U.S. had shown that ultraviolet light causes mutations at points n a DNA strand containing specific nucleotide bases. Bases are the variable parts of nucleotides and go by the names adenine (*A*), guanine (*G*), cytosine (*C*) and thymine (*T*). Ultraviolet light creates mutations where a so-called pyrimidine base—cytosine or thymine—lies adjacent to another pyrimidine. About two thirds of these mutations are *C*-to-*T* substitutions, and about 10 percent of these changes occur at two adjacent *C*s, with both bases changing to *T*s. These features of the mutations created by ultraviolet light constitute a fingerprint of sorts, because they are made by no other agents.

We thus had a good idea of the kinds of distinctive mutations that should result from exposure to sunlight. But we needed to pinpoint which of the vast number of human genes mutated to produce a carcinogenic effect. Our best guess was that the solution lay with the handful of human genes already known to be involved in cancer.

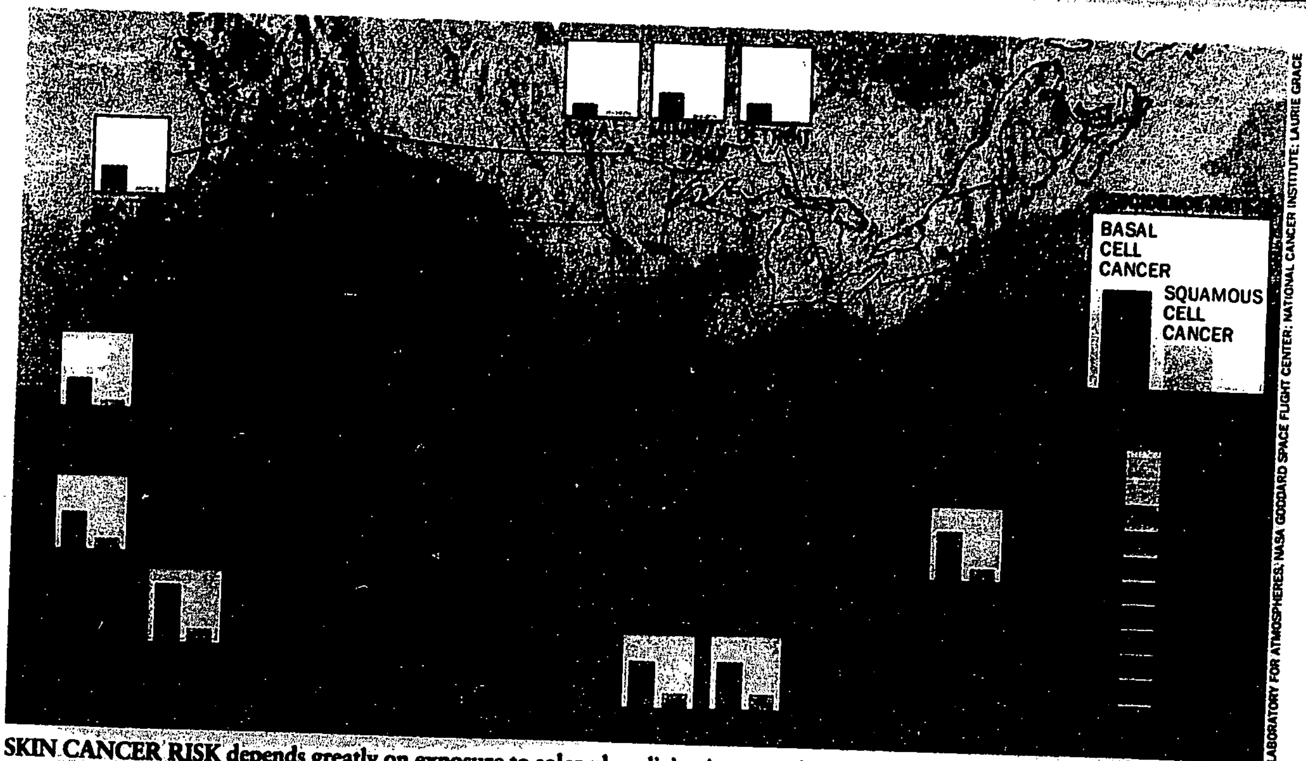
Of the recognized oncogenes and tumor suppressor genes, we chose to examine a tumor suppressor gene called *p53*, which is now known to be mutated in more than half of all people's cancers. At the time, we suspected that *p53* might be involved in many cases of skin cancer because of an intriguing connection between nonmelanoma skin cancer and a rare affliction (epidermodysplasia verruciformis) that causes wartlike growths to appear on the skin.

Previous research had revealed that such growths contain DNA from the human papillomavirus and that when these growths are located on sun-exposed skin, they can progress to basal cell or squamous cell cancer. Peter M. Howley and his colleagues at the Nati nal Cancer Institute had further shown that one f the proteins made by the papill mavirus inactivates the p53 protein. (Genes give rise to proteins, and the p53 protein, as might be expected, is the product of the *p53* gene.) So all indications were that *p53* might play a special role in nonmelanoma skin cancer. But we needed solid confirmation.

To find that proof, we studied squamous cell carcinomas, tumors unquestionably linked to sunlight (they occur on the face and hands, especially among whites living in the tropics). In collaboration with Jan Pontén of Uppsala University Hospital in Sweden, we discovered that more than 90 percent of the squamous cell carcinomas from a set of samples collected in the U.S. had a mutation somewhere in the *p53* tumor suppressor gene. These mutations occurred at sites with adjacent pyrimidine bases, and they had the distinctive *C*-to-*T* pattern associated with ultraviolet exposure. Our research group, along with several others, later pinpointed sunlight-related *p53* mutations in basal cell carcinomas as well. (Melanoma does not appear to be associated with alterations to *p53*. Researchers are still studying cancerous melanocytes for genes affected by sunlight.) After examining samples in our laboratory, Annemarie Ziegler found that precancerous skin also contains mutations of *p53*, indicating that the genetic changes occur long before



repair. If sunlight later burns unaltered cells (*c*), massively damaged cells will commit "cellular suicide" and be replaced by cells derived from healthy skin nearby (*d*). But if sunlight burns tissue near a *p53*-mutated cell that cannot self-destruct (*e*), the mutated cell may replace the dying, sunburned cells with its own progeny (*f*), thereby promoting growth f a tumor.



LABORATORY FOR ATMOSPHERES, NASA GODDARD SPACE FLIGHT CENTER; NATIONAL CANCER INSTITUTE; LAURIE GRACE

SKIN CANCER RISK depends greatly on exposure to solar ultraviolet radiation. Satellite measurements of ozone and cloud cover allow atmospheric scientists to estimate the amount of DNA-damaging ultraviolet light that reaches Earth's surface (shown here as an average for July 1992). Light-skinned people living in parts of the U.S. exposed to intense ultraviolet rays during the summer months are most prone to skin cancer, because they produce less of the melanin pigment that protects dark skin from ultraviolet damage. The bar graphs show incidence rates for nonmelanoma skin cancer in whites.

tumors appear. But were these mutations truly the cause of nonmelanoma skin cancer, or were they simply an irrelevant indicator of lifetime exposure to sunlight?

We could rule out this last possibility by the particular way the genetic code had been altered. The nucleotides in genes are arranged in well-defined codons—groups of three bases that specify different amino acids. The sequence of codons in a gene determines the sequence of amino acids that are strung together to construct a protein. But different codons can sometimes specify the same amino acid—as if the name of the amino acid could be spelled any of several ways. Typically the amino acid does not change when the first two bases of the codon are constant and only the third varies. Hence, if the *p53* mutations found in skin cancer were just a random effect of exposure to the sun, we would expect to find changes in the third position occurring as often as in the first or second. That is, there would be plenty of examples where the codon mutated (underwent a nucleotide base substitution) without altering its corresponding amino acid. Yet studies of this gene in skin cancers from around the globe had consistently revealed mutations that modified one or more amino acids in the p53 protein. These genetic changes to *p53*, then, were not just a side effect of ultraviolet exposure. They were in fact causing the skin cancers.

To better understand how the *p53* gene was affected in nonmelanoma skin cancer, we investigated whether certain segments of the *p53* gene were particularly prone to the mutation by sunlight of adjacent pyrimidine bases (that is, Cs or Ts). Biologists have found so-called mutation hot spots (places on a DNA strand where mutations tend to occur) whenever they expose living cells to carcinogens. After analyzing many tumors, we determined that the *p53* gene in nonmelanoma skin cancer contains about nine hot spots. In cancers unrelated to sunlight (such as colon or bladder cancer), five codons of *p53* are most often mutated, three of which are among the hot spots in skin cancers. At the two hot spots found only in the other cancers, the mutating *C* is flanked on either side by a *G* or *A* but never by a *T* or another C. Lacking a pair of pyrimidine bases, equivalent sites on the DNA of skin cells are protected from mutation by ultraviolet light.

Of the hundreds of places on the *p53* gene with adjacent pyrimidines, why do only a few sites act as hot spots when cells are exposed to sunlight? Several researchers have recently helped answer that question by building on a discovery made more than three decades ago at Oak Ridge National Laboratory by Richard B. Setlow and William L. Carrier. Setlow and Carrier determined that cells can reverse ultraviolet damage to their DNA by an enzymatic process called excision repair. Cells essentially snip out disrupted bases and replace them with intact ones. Working in our lab in 1992, Subrahmanyam Kunala showed that cells repair damage particularly slowly at some pyrimidine pairs. Subsequently, Gerd P. Pfeifer and his colleagues at the City of Hope Beckman Research Institute in Duarte, Calif., found that cells repair the *p53* sites mutated in nonmelanoma skin cancer more sluggishly than they do many other sites in the gene. Hence, it seems quite likely that the hot spots we found for skin cancer owe their existence to an inability of skin cells to mend these sites efficiently.

Cellular Proofreading

Even after we had identified the relevant *p53* mutations, the story of carcinogenesis remained woefully incomplete. After all, genes do not get cancer—cells do. It was clear enough that the p53 protein must operate in normal

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skin cells to prevent cancer, but how? One hint was available from Michael B. Kastan of Johns Hopkins Hospital. He found that cells subjected to x-rays stepped up production of the p53 protein, which in turn prevented the cells from dividing. Peter A. Hall and David P. Lane of the University of Dundee and Jonathan L. Rees of the University of Newcastle have shown a similar effect on the p53 protein in skin cells exposed to ultraviolet radiation. Cancer researchers speculate that the p53 protein normally stops a DNA-damaged cell from reproducing until it has had time to make repairs.

Moshe Oren and his colleagues at the Weizmann Institute of Science in Israel have proposed another function for the p53 protein as well: it can prevent cancer in situations where the DNA damage is too extensive to be repaired. They find that elevated levels of the p53 protein in a cell lead to apoptosis—programmed cell death. (Such cell death is a normal part of many biological processes, including embryonic development.) In this case, "suicide" of a sun-damaged cell would prevent it from becoming cancerous by permanently erasing its genetic mistakes. Such apoptosis could be called cellular proofreading. Because the skin sheds cells routinely, we surmised that skin cells often used *p53* in this way. But even before we began to test our idea, some evidence was already available to support it.

Dermatologists have recognized for a long time that when skin is sunburned, some cells come to resemble apoptotic cells. By 1994 we could show that sunburned cells contained breaks in their DNA similar to those in other apoptotic cells. The sunburned cells thus appeared t be in the process of c mmitting cellular suicide, and we began immediately to wonder whether cells that had l st *p53* could undergo such self-inflicted death.

At about the time we arrived at this investigative juncture, Tyler Jacks and his colleagues at the Massachusetts Institute of Technology had developed mice lacking the *p53* gene. When Alan S. Jonason and Jeffrey A. Simon irradiated the skin of these so-called *p53* knockout mice in our laboratory, they found far fewer sunburned, apoptotic cells than in normal mice exposed to the same ultraviolet radiation. Mice in which the *p53* gene had been only partially inactivated had only a moderate tendency to undergo light-induced cell suicide. These results suggested that programmed cell death was important for preventing nonmelanoma skin cancer and that loss of *p53* could block this process.

Double Punch from Sunlight

It is now possible to envision how the failure of cellular proofreading would lead to skin cancer. Normal skin exposed to sunlight will accumulate DNA damage caused by the ultraviolet B part of the solar spectrum. Cells unable to repair their DNA in a timely fashion die through apoptosis. But if the *p53* gene in a cell has mutated during a previous episode of exposure to sunlight, that cell will resist such self-destruction—even if it has been badly injured.

The situation is actually much worse. A cell on the verge of becoming cancerous is surrounded by normal cells that undergo apoptosis when damaged. The dying cells thus must be leaving some space into which the *p53*-mutated cell can grow. By inducing healthy cells to kill themselves ff, sunlight favors the proliferation of *p53*-mutated cells. In effect, sunlight acts twice to cause cancer: once to mutate the *p53* gene and then afterward to set up conditions for the unrestrained growth of the altered cell line. These tw actions, mutation and tumor promotion, are the one-two blows of carcinogenesis. Although mutation and promotion are carried out by separate agents in other tumors, in skin cancer ultraviolet radiation appears to throw both punches.

There are undoubtedly other genes involved in the development of skin cancer as well as other effects of sunlight that researchers do not yet fully understand. For example, medical researchers know that Gorlin syndrome (a disease in which patients have multiple basal cell cancers) is caused by an inherited mutation in a different tumor suppressor gene. With further investigation, the various mechanisms of carcinogenesis will become even more clear, and scientists may find clever ways to interrupt the progression of normal skin cells to cancerous ones.

It is not beyond reason to hope that the detailed understanding researchers are gaining of nonmelanoma skin cancer will yield new kinds of therapies. Perhaps drugs that restore normal function to a mutated p53 protein will allow doctors to offer their patients an effective remedy that does not involve surgery. Such a cure, perhaps administered as a simple skin cream that is absorbed by the affected cells, might be available within the next decade or two. If so, it will be of great benefit to countless aging members of the sun-loving baby-boom generation—a group to which we both admittedly belong.

The Authors

DAVID J. LEFFELL and DOUGLAS E. BRASH have worked together for nearly a decade to understand the role of the sun in causing skin cancer. Leffell, a professor of dermatology and surgery at the Yale School of Medicine, has brought to their research collaboration the experience gained in clinical practice. He earned his M.D. at McGill University in 1981 and trained at Cornell Medical School, Memorial Sloan-Kettering Cancer Center and the University of Michigan before taking a position on the faculty at Yale in 1988. Brash, too, is on the medical school faculty at Yale, and his credentials include a bachelor's degree in engineering physics from the University of Illinois. He shifted from engineering to the study f biophysics at Ohio State University, where he received his Ph.D. in 1979. Thereafter Brash pursued postdoctoral training in microbiology (at the Harvard School of Public Health) and pathology (at Harvard Medical School) until 1984. He spent the next five years at the National Cancer Institute before moving to Yale.

Further Reading

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Genes And Cancer Risk

Inherited mutations in these genes confer a very high cancer risk. Red type indicates cancer most often associated with mutation in the listed gene.

GENE		TUMOR TYPE	GENE CLASS
BREAST CANCER	*BRCA1*	Breast, ovary	Tumor suppressor
	BRCA2	Breast (both sexes)	Tumor suppressor
	p53	Breast, sarcoma Tumor	suppressor
COLON CANCER	*MSH2*	Colon, endometrium, other	Mismatch repair
	MLH1	Colon, endometrium, other	Mismatch repair
	PMS1,2	Colon, other	Mismatch repair
	APC	Colon	Tumor suppressor
MELANOMA	*MTS1 (CDKN2)*	Skin, pancreas	Tumor suppressor
	CDK4	Skin	Tumor suppressor
NEUROENDOCRINE CANCER	*NF-1*	Brain, other	Tumor suppressor
	NF-2	Brain, other	Tumor suppressor
	RET	Thyroid, other	Oncogene
KIDNEY CANCER	*WT1*	Wilms' tumor	Tumor suppressor
	VHL	Kidney, other	Tumor suppressor
RETINOBLASTOMA	*RB*	Retinoblastoma, sarcoma, other	Tumor suppressor

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Signal transduction through neuropeptide receptors

Zurück zur Übersicht "Forschung"

KET/p63: Splice variant analysis and regulation in keratinocytes

Hartwig Schmale, Casimir Bamberger, Julia Bethge, Heidje Christiansen

The human p63 gene is a member of the p53 gene family comprising the three proteins p53, p63 and p73. p63 is abundantly expressed in proliferating basal cells of the epidermis. p63 knock out-mice lack all squamous epithelia and they have severe limb truncations. In humans, mutations in p63 are the cause for hand and feet anomalies in autosomal dominant disorders such as the EEC (ectrodactylyl , ectodermal dysplasia, and facial clefts) syndrom.

In contrast to p53, the role of p63 in tumorigenesis is not yet clear. We have identified one missense mutation in the DNA-binding domain of p63 in 31 basal cell carcinomas studied. The low frequency of mutation suggests that the main biological role of p63 is not in carcinogenesis.

While only one p53 form is known, multiple isoforms of p63 and p73 have been described. The isoforms are generated by alternative splicing and by usage of different promotors. We have identified several tissue specific variations of exon 1 resulting in different amino-terminal ends. Transactivation properties of the splice variants inversely correlated with the length of the N-termini. Expression of a major KET variant appears to be a cell-type specific rather than a differentiation specific phenomenon.

The epidermis of p63 knock out-mice undergoes an unusual process of non-regenerative differentiation possibly caused by the loss of the proliferative potential of epidermal keratinocytes. We have studied the expression pattern of p63 in primary keratinocyte culture during autocrine terminal differentiation. The major isoform in proliferating keratinocytes is p63deltaN which lacks exons 2 and 3 coding for the transactivation domain. We showed a reduction of p63deltaN expression in keratinocyte culture when the cells began to differentiate. Treatment of primary human keratinocytes with all-trans retinoic acid prevents downregulation of p63 during autocrine terminal differentiation. These data suggest that p63 expression in human keratinocytes affected by all-trans retinoic acid might contribute to the fine tuned keratinocyte proliferation and differentiation equilibrium in the mammalian epidermis.

Collaborations

Dieter Pollet, Paul Gerson Unna-Skin Research Center, Beiersdorf AG, Hamburg
Wolfgang Meyerhof, Deutsches Institut für Ernährungsforschung, Potsdam, Germany

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Letzte Änderungen: 4. Juli 2001, Arne Blichenberg

UVB-induced Cyclobutane Pyrimidine Dimer Frequency Correlates with Skin Cancer Mutational Hotspots in *p53*

Régen Drouin and Jean-Philippe Therrien

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ABSTRACT

Ultraviolet light has been identified as the major carcinogen in skin cancer and the *p53* tumor suppressor gene is a major target for UV-induced mutations. The mutations are probably caused by unrepaired UV-induced cyclobutane pyrimidine dimers (CPD) and possibly by the less frequent pyrimidine (6-4) pyrimidone photoproducts. While hot spots for *p53* mutations in human nonmelanoma skin tumors correspond quite well to slow spots for CPD repair in cultured cells irradiated with the model mutagen 254 nm UVC (which is not present in terrestrial sunlight), they do not all coincide with sequences that are initially frequently damaged by 254 nm UVC. Using LMPCR (ligation-mediated polymerase chain reaction), we show that environmentally relevant UVB light induces CPD at CC and PyrmC positions much more frequently than does UVC light, and that all eight skin cancer hot spots in *p53* are also hot spots for UVB-induced CPD. Our results show that methylation of dipyrimidine sites (PyrmCpG) is associated with an increase rate of CPD formation upon UVB irradiation. Consequently, DNA methylation may increase the mutagenic potential of UVB and explains that several *p53* mutation hot spots are found at PyrmCpG. The distribution patterns of CPD formation and the photofootprint patterns found along exons 5 and 6 of *p53* gene are suggestive of DNA folding into nucleosomes.

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UVB-induced Cyclobutane Pyrimidine Dimer Frequency Correlates with Skin Cancer Mutational Hotspots in *p53*

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ABSTRACT

Ultraviolet light has been identified as the major carcinogen in skin cancer and the *p53* tumor suppressor gene is a major target for UV-induced mutations. The mutations are probably caused by unrepaired UV-induced cyclobutane pyrimidine dimers (CPD) and possibly by the less frequent pyrimidine (6-4) pyrimidone photoproducts. While hot spots for *p53* mutations in human nonmelanoma skin tumors correspond quite well to slow spots for CPD repair in cultured cells irradiated with the model mutagen 254 nm UVC (which is not present in terrestrial sunlight), they do not all coincide with sequences that are initially frequently damaged by 254 nm UVC. Using LMPCR (ligation-mediated polymerase chain reaction), we show that environmentally relevant UVB light induces CPD at CC and PyrmC positions much more frequently than does UVC light, and that all eight skin cancer hot spots in *p53* are also hot spots for UVB-induced CPD. Our results show that methylation of dipyrimidine sites (PyrmCpG) is associated with an increase rate of CPD formation upon UVB irradiation. Consequently, DNA methylation may increase the mutagenic potential of UVB and explains that several *p53* mutation hot spots are found at PyrmCpG. The distribution patterns of CPD formation and the photofootprint patterns found along exons 5 and 6 of *p53* gene are suggestive of DNA folding into nucleosomes.

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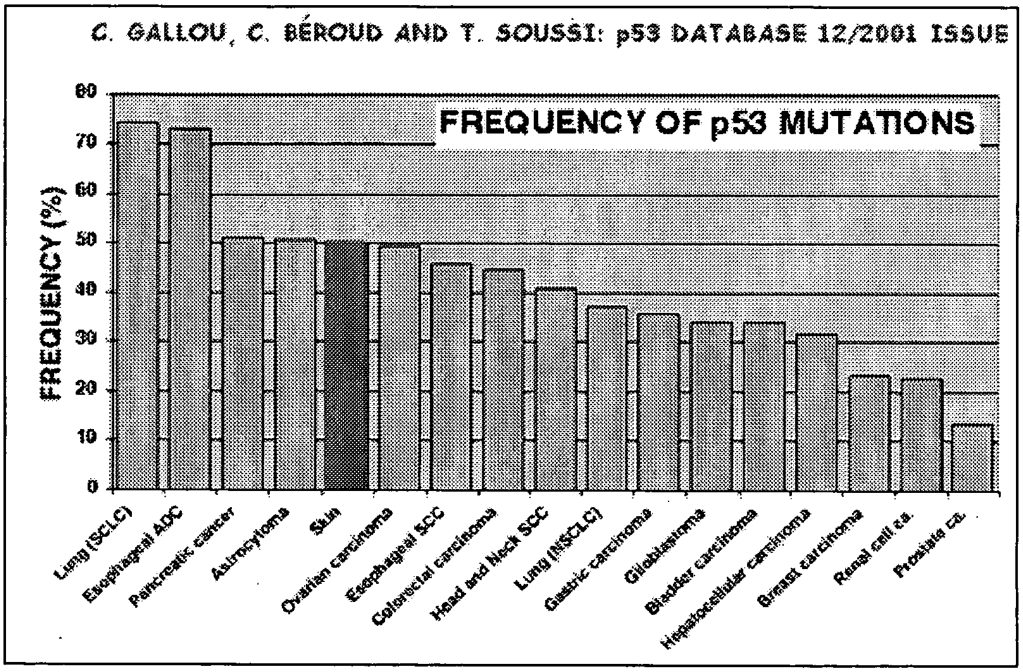
p53 IN SKIN CANCER



FREQUENCY OF p53 MUTATIONS IN SKIN CANCER

Basal cell carcinoma is the most common form of skin cancer. The second most common type of skin malignancy is squamous cell carcinoma. Although these 2 types of skin cancer are the most common of all malignancies, they account for less than 0.1% of patient deaths due to cancer. Both of these types of skin cancer are more likely to occur in individuals of light complexion who have had significant exposure to sunlight, and both types of skin cancers are more common in the southern latitudes of the Northern hemisphere. The overall cure rate for both types of skin cancer is directly related to the stage of the disease and the type of treatment employed. However, since neither basal cell carcinoma nor squamous cell carcinoma of the skin are reportable diseases, precise 5-year cure rates are not known. Although basal cell carcinoma and squamous cell

carcinoma are by far the most frequent types of skin tumors, the skin can also be the site of a large variety of malignant neoplasms. These other types of malignant disease include malignant melanoma, cutaneous T-cell lymphomas (mycosis fungoides), Kaposi's sarcoma, extramammary Paget's disease, apocrine carcinoma of the skin, and metastatic malignancies from various primary sites

Basal cell carcinoma and squamous cell carcinoma are both of epithelial origin. They are usually diagnosed on the basis of routine histopathology. Squamous cell carcinoma is graded 1 to 4 based on the proportion of differentiating cells present, the degree of atypicality of tumor cells, and the depth of tumor penetration. Apocrine carcinomas, which are rare, are associated with an indolent course and usually arise in the axilla.

Basal cell carcinoma

Basal cell carcinoma is at least 3 times more common than squamous cell carcinoma in nonimmunocompromised patients. It usually occurs on sun exposed areas of skin, and the nose is the most frequent site. Although there are many different clinical presentations for basal cell carcinoma, the most characteristic type is the asymptomatic nodular or nodular ulcerative lesion that is elevated from the surrounding skin and has a pearly quality and contains telangiectatic vessels. It is recognized that basal cell carcinoma has a tendency to be locally destructive. High-risk areas for tumor recurrence include the central face (periorbital region, eyelids, nasolabial fold, nose-cheek angle), postauricular region, pinna, ear canal, forehead, and scalp. A specific subtype of basal cell carcinoma is the morphea-form type. It typically appears as a scar-like, firm plaque and because of indistinct clinical tumor margins, it is difficult to treat adequately with traditional treatments.

Squamous cell carcinoma

Squamous cell tumors also tend to occur on sun-exposed portions of the skin such as the ears, lower lip, and dorsa of the hand. However, squamous cell carcinomas that arise in areas of non-sun-exposed skin or that originate de novo on areas of sun-exposed skin are prognostically worse since they have a greater tendency to metastasize. Chronic sun damage, sites of prior burns, arsenic exposure, chronic cutaneous inflammation as seen in long standing skin ulcers, and sites of previous x-ray therapy are predisposed to the development of squamous cell carcinoma.

Actinic keratosis

Actinic keratoses are potential precursors of squamous cell carcinoma. These typical red

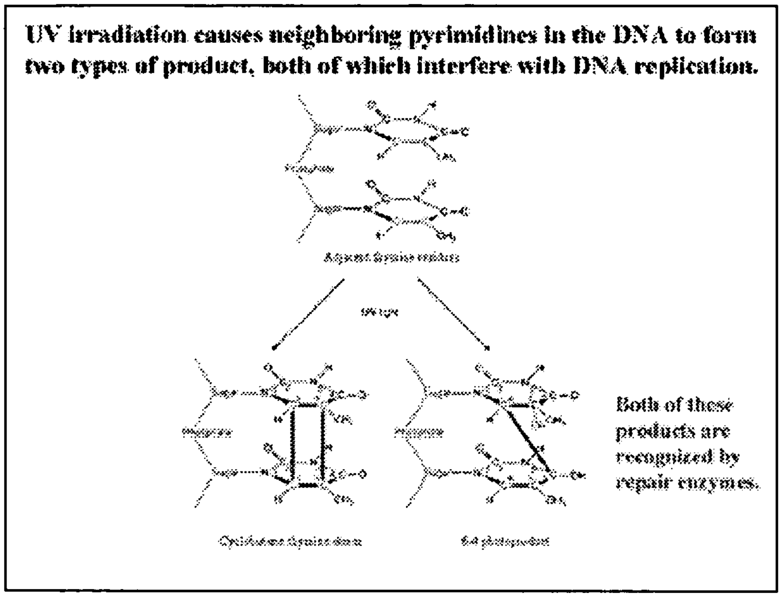
scaly patches usually arise on areas of chronically sun-exposed skin, and are likely to be found on the face and dorsal aspects of the hand. Although the vast majority of actinic keratoses do not become squamous cell carcinomas, it is thought that as many as 5% of actinic keratoses will evolve into this locally invasive carcinoma. Due to this premalignant potential, the destruction of actinic keratoses is advocated.

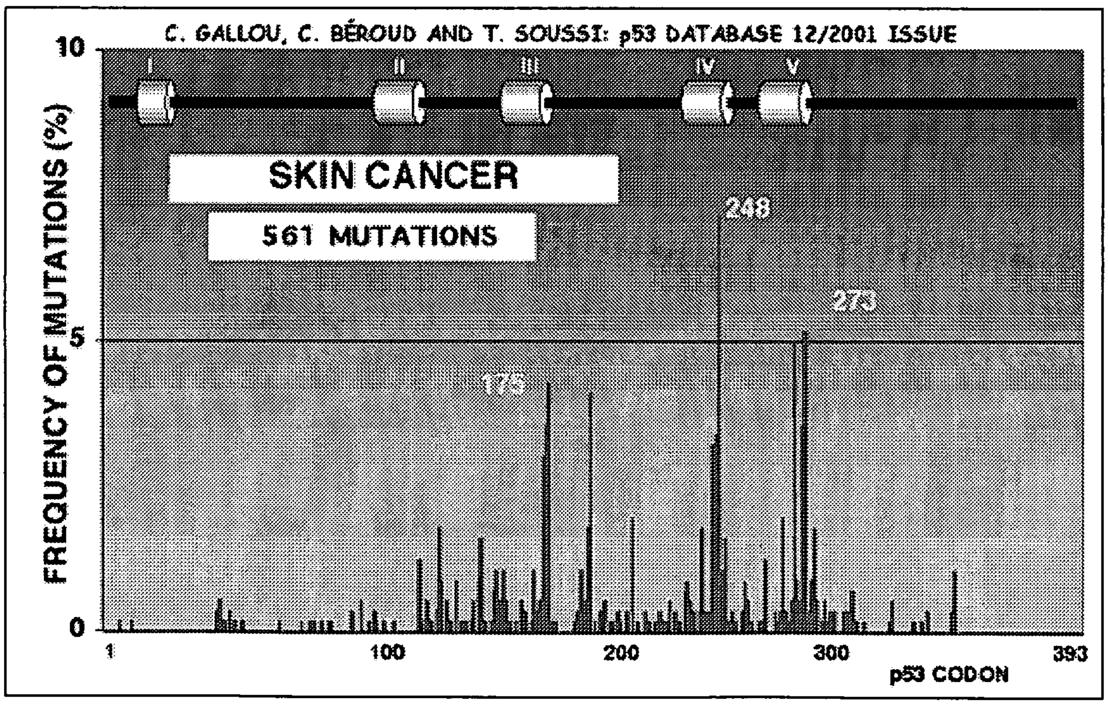
UV radiation-induced mutations have been studied in various animal models. The majority of the mutations are found to be located at dipyrimidine sites (i.e. (T-T, C-C, C-T or T-C) and correspond to a C to T transition. More than 20% correspond to tandem mutations involving the two adjacent nucleotides of the dipyrimidine sites (C-C to T-T).

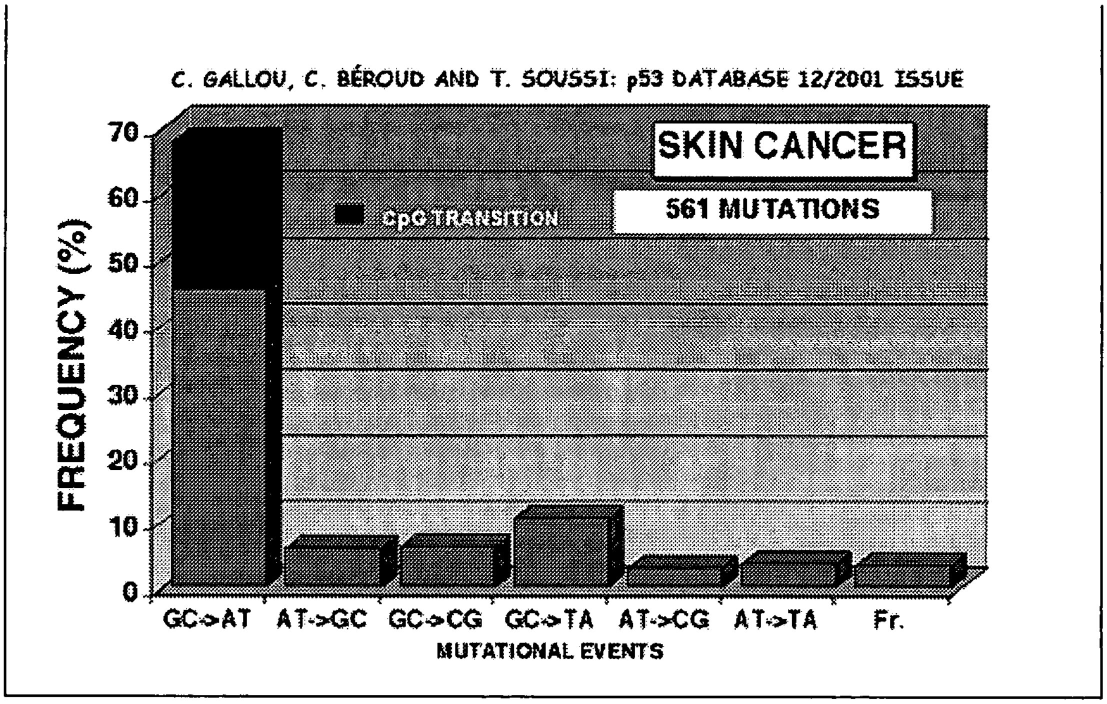
Several human genetic syndromes are associated with DNA repair deficiency. Among them, xeroderma pigmentosum (XP) is an autosomal, recessively inherited disease. Patients with XP show clinical and cellular hypersensitivity to UV radiation, resulting in a very high incidence of skin cancer. In these subjects, the median age of onset of skin cancer is 8 years, nearly 50 years younger than in the general population.

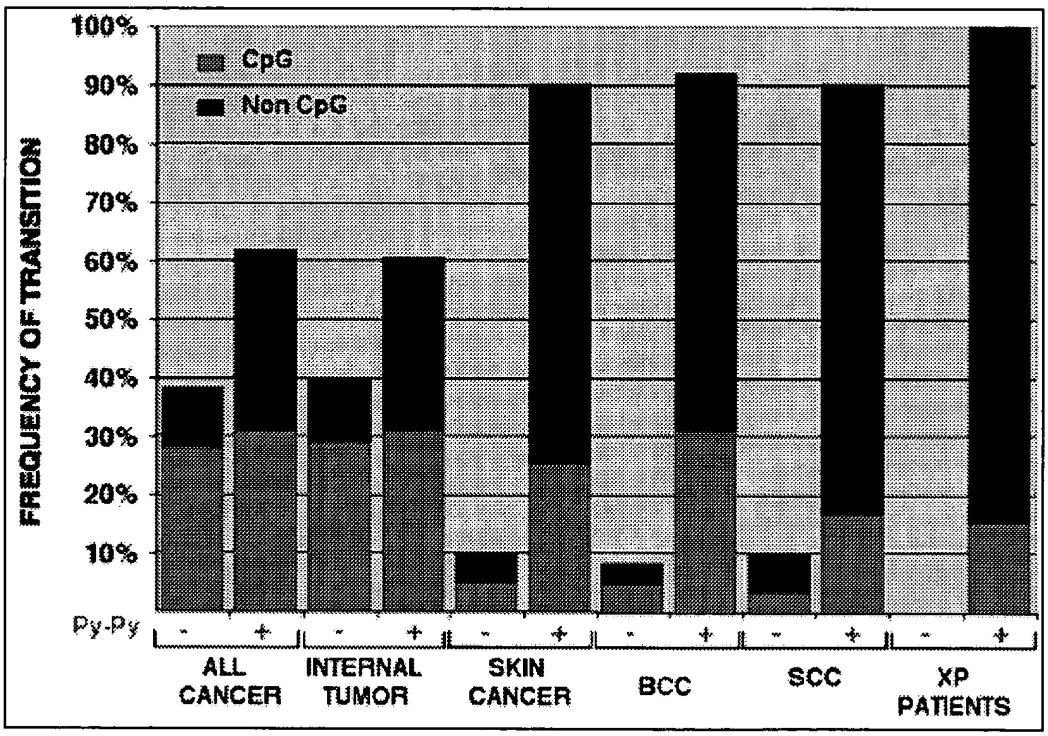
Brash et al. showed that, in skin spinocellular cancer, C ---> T mutations predominate in pyrimidine dimers. It is well known that ultraviolet radiation, an etiological agent of most skin cancers, acts directly on these dimers. A particular characteristic of the action of UV radiation is the change in the bases CC ---> TT, observed in Brash's series but also in other skin cancer series such as basocellular cancers (Rady et al. 1992). In patients with genetic DNA repair deficiencies, such as xeroderma pigmentosum (XP), the phenotype is much more marked. All mutations found in skin cancers are located on the pyrimidine dimers and 55 % are tandem mutations CC ---> TT (Dumaz et al. 1994). This type of mutation is only very rarely found in internal cancers (less than 1 %). In skin cancers from XP patients, more than 95 % of the mutations are located on the noncoding strand of the p53 gene, while in other skin tumors and in internal cancers, no special trends are observed. This result therefore suggests that there is preferential repair of the coding strand, which has been confirmed by Toranaletti and Pfeifer, who showed that the repair rate of pyrimidine dimers in the p53 gene is highly variable, with an especially low rate in the codons that are often mutated in skin cancer. Such p53 mutations seem to be very early events as they can be found both in precancerous lesions such as actinic keratosis (Ziegler et al. 1994) and in normal skin exposed to UV (Jonason et al. 1996). Recent work have demonstrated that human epidermal cancer and accompanying precursors have identical p53 mutations different from p53 mutations in adjacent areas of clonally expanded non-neoplastic keratinocytes (Ponten et al. 1997; Ren et al. 1997; Ren et al. 1996; Ren et al. 1997; Ren et al. 1996).

These results taken together (predominance of CC -> TT lesions on the non coding strand) were experimentally confirmed in animals carrying UV-induced tumors (Dumaz et al. 1997; Kress et al. 1992).



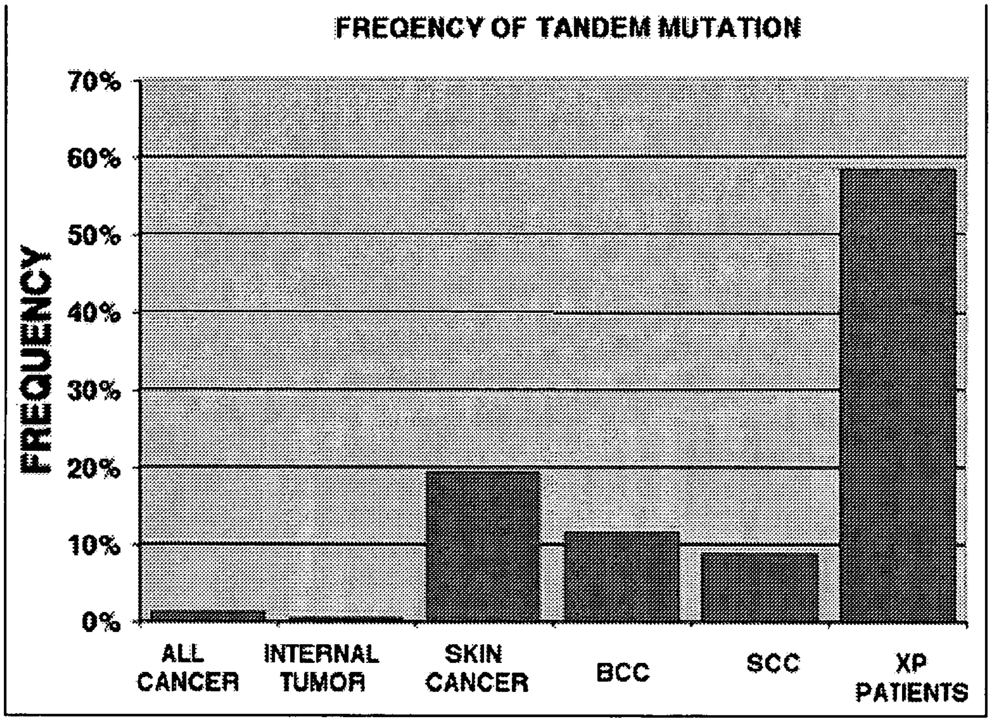






Transition at Py-Py site in Skin cancer

BCC: basal cell carcinoma; SCC: squamous cell carcinoma of the skin: XP: xeroderma pigmentosum patients.



Tandem mutation in Skin cancer

BCC: basal cell carcinoma; SCC: squamous cell carcinoma of the skin: XP: xeroderma pigmentosum patients.

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This site was updated: **December 2001**

Improvements or Questions ? mail me : thierry.Soussi@curie.fr

VISIBLE GENETICS

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These pages are designed with investors in mind and include information on the co
performance.

September 4, 1996

Visible Genetics Inc.
For Immediate Release

Contact:
For Visible Genetics Inc.
John K. Stevens, Chairman and C.E.O.
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VISIBLE GENETICS INC. RECEIVES U.S. PATENTS FOR P53 AND R CANCER GENE TESTS

TORONTO, ONTARIO (September 4, 1996): Visible Genetics Inc. (VGI, VGINF) today announced the issuance of two U.S. patents covering me test kits that permit the rapid, inexpensive detection of mutations in tw associated with human cancers. The first, U.S. Patent No. 5,545,527, c **p53** GeneKit, which allows users to quickly and inexpensively detect p mutations in the DNA code of the **p53 gene**. The second, U.S. Patent 5,550,020, covers the RB1 GeneKit, which allows users to search for p mutations in the RB1 **gene** from a simple blood sample.

Mutations in the **p53 gene** are found in a wide variety of tumors, inc about 70% of colorectal cancers, 50% of lung cancers, and 40% of bre cancers. Moreover, aberrant forms of the **p53 gene** are reported to co with more aggressive tumors, metastasis and lower 5-year survival rat reports have emerged for cancers of the colon, lung, cervix, bladder, p breast and **skin**. Visible Genetics is developing its **p53** GeneKit in colla with Eleftherios P. Diamandis, M.D. of the Mt. Sinai Hospital in Toronto Diamandis comments, "The serious consequences of **p53 gene** mutati mandate a method of diagnosis that is rapid, accurate, and can be per the earliest stage of tumor development. There are literally millions of patients in North America who may benefit from use of this test."

RB1 mutations lead to retinoblastoma, a potentially curable eye canc children that is invariably fatal unless the tumor is destroyed at an ear eliminated by removal of the affected eye. Typically, children born to a families are repeatedly screened for the tumor using highly invasive m costing thousands of dollars. A report by Brenda Gallie, M.D. of Toront for Sick Children and the Eye Research Institute of Canada in the Augu the American Journal of Human Genetics illustrates the potential for RB diagnostics to avoid trauma for infants and save health care dollars for That study shows that a savings of up to $16,611 could be realized pe using DNA diagnostics to detect RB1 mutations instead of conventiona

using DNA diagnostics to detect RB1 mutations instead of conventiona of retinoblastoma diagnosis. Dr. Gallie is currently collaborating with V Genetics on the development of the RB1 GeneKit.

Both the RB1 and **p53** GeneKits apply the Stratified Matrix methodol the subject of U.S. Patent 5,545,527, also recently issued to Visible Ge This technology represents a fundamental departure from the convent manner in which individual assays for genetic mutations have been pe separate tests. Many individual assays may have low accuracy alone, b combined in a Stratified Matrix can produce a highly reliable and accur diagnostic test with a significant reduction in the testing cost per patie

John Stevens, Chairman and Chief Executive Officer of Visible Geneti "The RB1 and **p53** GeneKits illustrate the value of Stratified Matrix as technology for the development of a variety of clinical DNA diagnostics

Visible Genetics, Inc. develops, manufactures and markets high perfor automated diagnostic DNA sequencing systems for genes linked to dise company's OpenGene™ system employs stratified DNA testing to signific reduce the time and cost involved in finding and identifying disease-ca genetic mutations.

Atlas of Genetics and Cytogenetics in Oncology and Haematology

P53 (Protein 53 kDa)

Identity

Other names	**TP53 (Tumour Protein 53)**
Hugo	TP53
Location	17p13

DNA/RNA

Description	the gene encompasses 20 kb of DNA; 11 exons (the first is non-coding).
Transcription	3.0 kb mRNA; 1179 bp open reading frame.

Protein

Description	393 amino acids ; 53 kDa protein ; numerous post translational modifications, phosphorylation, acetylation, ubiquitination; contains from N-term to C-term, a transactivation domain ((1-42), a Proline rich domain (63-97), a specific DNA binding domain (102-292), 3 nuclear localization signals (305-322), a tetramerization domain that include a nuclear export signal (325-355) and a negative regulatory domain (360-393)
Expression	widely expressed.
Localisation	nucleus.
Homology	the five domains are highly-conserved regions between species (from human to fly). Two new genes homologous to p53 have been discovered, p73 localized at 1p36 and p63 localized at 3q27.

Mutations

Germinal	in Li-Fraumeni syndrome, a dominantly inherited disease in which affected individuals are predisposed to develop sarcomas, osteosarcomas, leukemias and breast cancers at unusually early ages.
Somatic	P53 is mutated in about 50% of human cancers, and the non-mutated allele is generally lost; the frequency and the type of mutation may vary from one tumour type to another; these mutations are missense (80%), non-sense (7.5%), deletions, insertions or splicing mutations (12.5%) ; there are some hot-spots for mutations at CpG dinucleotides at positions 175, 248, 273 and 282; P53 mutation is an adverse prognostic feature in a number of cancer, but not in all. Mutational events are related to carcinogen exposure in lung, liver and skin cancer.

Implicated in

Entity	Li-Fraumeni syndrome
Disease	autosomal dominant condition; cancer prone disease; Li-Fraumeni syndrome is defined by the existence of both a proband with a sarcoma and two other first-degree relatives with a cancer by age 45 years; a germline mutation of P53 is found in at least 50% of cases; germline mutation of the kinase CHK2, an activator of p53, has been discovered in several Li-Fraumeni families free of p53 mutation.
Prognosis	most common cancer in Li-Fraumeni children are : soft tissues sarcoma before the age of 5 yrs and osteosarcoma afterwards, and breast cancer in young adults; other frequent cancers: brain tumours, leukaemias, adrenocortical carcinoma; 1/3 of patients have developped more than one primary cancer, which is quite characteristic of Li-Fraumeni syndrome but may also be representative of Bloom's syndrome; cancers in this disease, as in other cancer-prone diseases, often occur early in life: 50% of patients aged 30 yrs have had a cancer (i.e. penetrance is 50%, according to this disease definition); and penetrance is 90% at age 60 yrs.
Oncogenesis	(known) germinal mutation are variable, but are mostly missense mutations located in exons 4 to 9 in tumours occurring in these patients, the other (wildtype) allele is lost, in accordance with the two-hit model for neoplasia, as is found in retinoblastoma.

Entity haematological malignancies

Oncogenesis **P53 gene** alterations have been found in : 20 - 30% of blast crisis CML (mostly in the myeloid type), often associated with i(17q); in 5% of MDS cases and 15% of ANLL often with a visible del(17p); in 2% of ALL (but with high variations according to the ALL type, reaching 50% of L3 ALL (and Burkitt lymphomas); in 15% of CLL (and 40% in the aggressive CLL transformation into the Richter's syndrome) and 30% of adult T-cell leukaemia (only found in the aggressive form), in 5-10% of multiple myelomas; in 60-80% of Hodgkin disease; in 30% of high grade B-cell NHL (rare in low grade NHL), and 50% of HIV-related NHL; **P53 gene** alterations in haematological malignancies are associated with a poor prognosis.

Entity lung cancers

Disease lung cancers are neuroendocrine lung tumours (small cell lung carcinomas, carcinoids, large cell neuroendocrine carcinomas) or non neuroendocrine lung tumours (squamous carcinomas, adenocarcinomas, large cell carcinomas).

Oncogenesis is multistep, through C-MYC or N-MYC activation, H-RAS1 or K-RAS2 mutation, **P53**, RB1, and P16 inactivation, loss of heterozygosity (LOH) at 3p, 13q, 17p; P 53 mutations, in this particular case, does not seem to have prognostic implication; **P53** is mutated in 30% of lung adenocarcinomas to 80% of small cell lung carcinomas; hotspots at codons 157, 158, 179, 245, 248 and 273. **p53** mutations in lung **cancer** from smoker have a very specific pattern related to carcinogen exposure (high frequency to GC->TA transversion and hot spot at codon 157 and 158).

Entity colorectal cancers

Disease there are two types of colorectal cancers, according to the ploidy: - the diploid form, RER+ (Replication Error+), sporadic, without loss of heterozygosity (LOH), with few mutations of **p53** and APC, and right-sided; -the polyploid form, RER-, with LOH (5q, 17p, 18q), mutations in **p53**, and more often left-sided, they have a worse prognosis.

Prognosis survival, although improving, is not much more than 50% after 5 years

Cytogenetics diploid tumours without frequent allelic losses; aneuploid tumours with numerous allelic losses; LOH on chromosomes 17 and 18 in more than 75% of cases; other chromosome arms losses in about 50% of cases.

Oncogenesis a number of genes are known to be implicated in tumour progression in colorectal cancers : APC, **P53**, KRAS2, mismatch repair genes (MMR genes); **P53** is mutated in 60-65% of colorectal **cancer** cases; mutations of **P53** are mostly located in exons 4 to 8 with hotspots at codons 175, 245, 248, 273 and 282

Entity bladder **cancer**

Prognosis highly variable, according to the stage and the grade

Cytogenetics -9, -11 or del(11p), del(17p) and LOH at 17p, del(13q), frequent other LOH, aneuploidy, polyploidy, complex karyotypes.

Oncogenesis multi-step and largely unknown process; loss of 9q and **P53** mutations would be early events; RB1, and P16 inactivation, EGFR overexpression, LOH at 3p, 8p, 11p, 13q,

17p, 18q; P53 is mutated in 40-60% of bladder cancer cases; P 53 mutations bear a prognostic implication.

Entity	breast cancer
Prognosis	P53 mutation bears a prognostic implication in N+ patients and is related to poor response to doxorubicin therapy.
Oncogenesis	P53 is mutated in 30% of breast cancers; preferentially observed in advanced and aggressive forms; probably a late event; hotspots at codons 175, 248, and 273. The frequency and pattern of p53 mutation in breast cancer is subject to important geographical variations.
Entity	skin cancers
Disease	skin cancers include basal cell carcinomas, squamous cell cercinomas, and melanomas.
Prognosis	highly different according to the pathological group
Oncogenesis	P53 is mutated in 40-60% of skin cancers; hotspots at codons 196, 248, 278. The pattern of p53 mutation in skin cancer is highly related to UV exposure.
Entity	oesophagus cancers
Disease	two main forms: squamous cell carcinoma and adenocarcinoma
Oncogenesis	P53 is mutated in 50% of oesophagus cancers (70% in squamous cell carcinoma and 45% of adenocarcinoma); probably an early event; hotspots at codons 175, 248 and 273. The pattern of p53 mutation is different in squamous cell carcinoma and adenocarcinoma
Entity	liver cancer
Cytogenetics	losses of 1p, 4q, 5p, 5q, 8q, 13q, 16p, 16q, and 17p in 20 to 50% of cases
Oncogenesis	specific mutation at codon 249 related to aflatoxin B1 dietary exposure in exposed area (China, Africa); low frequency of mutation in developed countries.
Entity	prostate cancer and other cancers (in progress)

To be noted

germinal mutations of P53 have also been found in families where the criteria for the Li-Fraumeni syndrome were not reached.

External links

Hugo	TP53	Genes Cyto	Gene Seq [Map View - NCBI]
GeneCards	TP53		
CancerGene	TP53		
GDB	TP53		
Genatlas	TP53		
LocusLink	TP53	AceView - NCBI	
GoldenPath	TP53 - 17p13		
Ensembl	TP53 - 17p13		
GeneLynx	TP53		
eGenome	TP53		
euGene	7157		
HomoloGene	TP53		
Genbank	M14695 [SRS]	M14695 [ENTREZ]	
RefSeq	M_000546 [SRS]	M_000546 [ENTREZ]	
RefSeq	NT_010687 [SRS]	NT_010687 [ENTREZ]	
Unigene	Hs.1846 [S RS]	Hs.1846 [NCBI]	HS1846 [spliceNest]
SwissProt	P04637 [SRS]	P04637 [EXPASY]	P04637 [INTERPRO]
PDB	1A1U [SRS]	1A1U [PdbSum],	1A1U [IMB]
Pfam	PF00870 [SRS]	PF00870 [Sanger]	pfam00870 [NCBI-CDD]
DOMO	P04637		
PRODOM	P04637 [Domain structure]	P04637 [sequences sharing at least 1 domain]	
BLOCKS	P04637		
Human PSD	TP53		
PubGene	TP53		
OMIM	191170		
SNP	TP53 [dbSNP-NCBI]		
SNP	M_000546 [SNP-NCI]	NT_010687 [SNP-NCI]	
SNP	TP53 [GeneSNPs - Utah]	TP53 [SNP - CSHL]	TP53] [HGBASE - SRS]
HGMD	120445		
Other database	The P53 Database		
Other database	HotMolecBase		
Probe	P53 (17p13.1) in normal cells (Bari)		
Probe	TP53 Related clones (RZPD - Berlin)		

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CancerGene Bibliographic Citations

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Sun and skin – a dangerous combination

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3. The molecular mechanisms of skin cancer

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The body kills skin cells that have been exposed to too much ultraviolet radiation. Bringing about cell death is the function of a protein called p53. When an ultraviolet ray hits the DNA within a gene that codes for p53, basal cell and squamous cell cancer can result.

When present in a high enough concentration, the p53 protein causes a cell to 'self-destruct'. This protein is normally produced in greater amounts after exposure to ultraviolet radiation. But after the radiation damages the gene for p53, the p53 protein that the gene makes is slightly altered and doesn't function correctly. The defective version of the protein cannot make a damaged cell die.

The gene for p53 only needs a very small change for a defective protein to be produced. This tiny error will be perpetuated whenever the cell divides. Eventually, many cells with the incorrect gene will exist.

The cells with the incorrect gene won't die when exposed to too much ultraviolet radiation. Instead they will reproduce, stimulated to do so because they find the normal cells around them dead. With each subsequent heavy exposure to too much sunlight, more normal cells will commit suicide, and the colony of cells with the damaged gene will multiply all the more. This is the beginning of a tumour.

So, by inducing cells carrying the normal p53 gene to kill themselves off, sunlight favours the proliferation of p53-mutated cells. Ultraviolet radiation is thus responsible for the two key steps in cancer generation: mutation and tumour promotion. The p53 gene and its protein are involved in the

development of basal cell carcinoma and squamous cell carcinoma, but not melanoma. A similar gene, p16, and its protein are thought to be involved in the development of melanoma, but these studies are preliminary.

Further reading

- ***Scientific American***, Vol. 275, no. 1, July 1996, pages 38-43
  *Sunlight and **skin cancer*** (by David J. Leffell and Douglas E. Brash)

Related site

- **DNA and genes (*Back to basics*, Australian Academy of Science)**

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Environmental Mutagens
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p53 Tumor Suppressor Gene: At the Crossroads of Molecular Carcinogenesis, Molecular Epidemiology, and Cancer Risk Assessment

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Abstract

Carcinogenesis is a multistage process involving the inappropriate activation of normal cellular genes to become oncogenes, e.g., *ras*, and the inactivation of other cellular genes called tumor suppressor genes. p53 is the prototypic tumor suppressor gene that is well suited as a molecular link between the causes of cancer, i.e., carcinogenic chemical and physical agents and certain viruses, and the development of clinical cancer. The p53 tumor suppressor gene is mutated in the majority of human cancers. Genetic analysis of human cancer is providing clues to the etiology of these diverse tumors and to the functions of the p53 gene. Some of the mutations in the p53 gene reþect endogenous causes of cancer, whereas others are characteristic of carcinogens found in our environment. In geographic areas where hepatitis B virus and a dietary chemical carcinogen, aþatoxin B_1, are risk factors of liver cancer, a molecular signature of the chemical carcinogen is found in the mutated p53 gene. A different molecular signature in the p53 gene is found in skin cancer caused by sunlight. Because mutations in the p53 gene can occur in precancerous lesions in the lung, breast, esophagus, and colon, molecular analysis of the p53 gene in exfoliated cells found in either body þuids or tissue biopsies may identify individuals at increased cancer risk. p53 mutations in tumors generally indicate a poorer prognosis. In summary, the recent history of p53 investigations is a paradigm in cancer research, illustrating both the convergence of previously parallel lines of basic, clinical, and epidemiologic investigation and the rapid translation of research findings from the laboratory to the clinic. -- **Environ Health Perspect** 104(Suppl 3):435-439 (1996)

Key words: p53 gene, molecular carcinogenesis, molecular epidemiology, cancer risk assessment

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